CATENT COOPERATION TRE. . Y

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PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

United States Patent and Trademark Office (Box PCT) Crystal Plaza 2 Washington, DC 20231 ÉTATS-UNIS D'AMÉRIQUE

Date of mailing (day/month/year)
29 January 1999 (29.01.99)

in its capacity as elected Office

International application No. PCT/SE98/00907

International filing date (day/month/year)

15 May 1998 (15.05.98)

J 1747-1 WO

Priority date (day/month/year)

30 May 1997 (30.05.97)

Applicant's or agent's file reference

Applicant

NYQVIST, Håkan et al

1.	The designated Office is hereby notified of its election made:
	X in the demand filed with the International Preliminary Examining Authority on:
	17 December 1998 (17.12.98)
	in a notice effecting later election filed with the International Bureau on:
2.	The election X was
	was not
	made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).
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The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland

Authorized officer

Nicola Wolff

Telephone No.: (41-22) 338.83.38

Facsimile No.: (41-22) 740.14.35

PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

J 1747-1 WO	ternational EA/416)
International Patent Classification (PC) or national classification and IPC6 C 07 D 311/58, A 61 K 31/35 Applicant Astra Aktiebolag et al 1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36. 2. This REPORT consists of a total of 4 sheets, including this cover sheet. This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authorit (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT). These annexes consist of a total of 4 sheets Sheets RECEN	
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VII Contain defeats in the interestinal configuration	
VII Certain defects in the international application	
VIII Certain observations on the international application	
Date of submission of the demand Date of completion of this report	
17.12.1998 30.08.1999	
Name and mailing address of the IPEA/SE Authorized officer	
Patent- och registreringsverket Telex	
S-102 42 STOCKHOLM PATOREG-S GÖRAN KARLSSON/ELS	ļ
Facsimile No. 08-667 72 88 Telephone No. 08-782 25 00 Form PCT/IPEA/409 (cover sheet) (January 1994)	

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/SE98/00907

L Basis of t	he report			
1. This report under Article	has been drawn or 14 are referred to in	n the basis of (Replacement she in this report as "originally filed"	ets which have been furnished and are not annexed to the re	to the receiving Office in response to an invitation port since they do not contain amendments.i:
	the international	application as originally file	d.	REC'D 2 2 SEP 1999
\boxtimes	the description,	pages <u>1-9</u>	, as originally filed,	WIDO
			, filed with the demand,	WIPO PCT
		· ·	, filed with the letter of	,
		pages	, filed with the letter of	
	the claims.	•	, as originally filed,	
			, as amended under Articl	le 19,
			, filed with the demand,	17.09.1998
			, filed with the letter of	,
\boxtimes	the drawings,	sheets/fig 1-2	as originally filed	
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		sheets/fig		
		sheets/fig	, filed with the letter of	
7. The amonds	nante hova raculta	d in the cancellation of:		
	the description,			
	the claims,	Nos.		
	·			
	the drawings,	sheets/fig		
3. This beyo	report has been es and the disclosure	stablished as if (some of) the as filed, as indicated in the su	amendments had not been upplemental Box (Rule 70.2)	made, since they have been considered to go (2(c)).
4. Additional	observations, if ne	ecessary:		

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/SE98/00907

III	No:	on-establishment of opinion with regard to novelty, inventive step and industrial applica	ability
The appl	que: licab	stions whether the claimed invention appears to be novel, to involve an inventive step (to be sle have not been examined in respect of:	non obvious), or to be industrially
[the entire international application,	
	\boxtimes	claims Nos. 11-14	
beca	iuse:		
	\boxtimes	the said international application, or the said claims Nos. $11-14$	
		relate to the following subject matter which does not require an international preliminary ex	xamination (specify):
		thod for treatment of the human or animal body Rule 67.1(iv)).	by therapy
Γ	\neg	the description, claims or drawings (indicate particular elements below) or said claims Nos	S.
L		are so unclear that no meaningful opinion could be formed (specify):	·
		the claims, or said claims Nos.	are so inadequately supported
		by the description that no meaningful opinion could be formed.	
Γ	\neg	no international search report has been establised for said claims Nos.	
<u> </u>	_	-	

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/SE98/00907

V.	Resoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability
	citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims Claims	1-10,15-17	YES NO
Inventive step (IS)	Claims Claims	1-10,15-17	YES NO
Industrial applicability (IA)	Claims Claims	1-10,15-17	YES NO

2. Citations and explanations

The invention relates to a salt (R)-3-N, N-diclobutylamino-8-fluoro-3,4-dihydro-2H-1-benzopyran-5-carboxamide hydrogen <math>(2R,3R)-tartate, processes for the manufacture of the salt, and pharmaceutical formulations for treatment of CNS disorders.

No relevant prior art has been found.

WO, A, 9511891 discloses the general state of the art, but is not considered to hinder a patent.

Therefore, the 17-09-1998 amended claims 1-10 and 15-17 are considered to fulfil the requirements of novelty, inventive step and industrial applicability.

PATENT COOPERATION TREATY

98 -02- 1999

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION CONCERNING AMENDMENTS OF THE CLAIMS

(PCT Rule 62 and Administrative Instructions, Section 417) To:

Swedish Patent Office P.O. Box 5055 Valhallavagen 136 S-102 42 Stockholm SUÈDE

Date of mailing (day/month/year)

29 January 1999 (29.01.99)

in its capacity as International Preliminary Examining Authority

International application No.

PCT/SE98/00907

International filing date (day/month/year) 15 May 1998 (15.05.98)

Applicant

ASTRA AKTIEBOLAG et al

The International Bureau hereby transmits a copy of the amendments to the claims under Article 19 together with any accompanying statement (Rule 62).

> The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland

Authorized officer

Nicola Wolff

Telephone No. (41-22) 338.83.38

Facsimile No. (41-22) 740.14.35



WIPO
- World Intellectual
Property Organization
34, Chemin des Colombettes
CH-1211 GENEVE 20
S c h w e i z

September 14, 1998

Our ref. J 1747-1 WO 3/12756

BY REGISTERED MAIL

Re: PCT/SE98/00907

With reference to PCT Article 19 and Rule 46 the applicant herewith files a new set of amended claims to be published together with the application.

Claim 1 in the originally filed International patent application has been deleted. In consequence the subsequent claims have been renumbered. The reason for the cancellation of the originally filed claim 1 is that said claim 1 has no correspondence in the priority application.

Please acknowledge receipt of this letter by return fax.

Astra AB

Britta Samuelsson .

e-mail: britta.samuelsson@astra.se.astra.com

CLAIMS

- 1. A salt (R)-3-N,N-dicyclobutylamino-8-fluoro-3,4-dihydro-2H-1-benzopyran-5carboxamide hydrogen (2R,3R)-tartrate.
 - 2. The salt (R)-3-N,N-dicyclobutylamino-8-fluoro-3,4-dihydro-2H-1-benzopyran-5-carboxamide hydrogen (2R,3R)-tartrate monohydrate.
- 10 3. The salt according to any one of claims 1 to 2 in substantially crystalline form.
 - 4. A pharmaceutical formulation containing, as active ingredient, the salt according to any one of claims 1 to 3 in association with a suitable diluent, excipient or an inert carrier.
- A pharmaceutical formulation according to claim 4 for oral administration.
 - 6. The salt according to any one of claims 1 to 3 for use in therapy.
- 7. The use of the salt according to any one of claims 1 to 3 in the manufacture of a medicament in the prevention or in the treatment of CNS disorders and related medical disturbances.
- 8. The use according to claim 7 in the manufacture of a medicament in prevention or in the treatment of 5-HT_{1A} receptor antagonist activity related CNS disorders and medical disturbances.
 - 9. The use according to claim 8 in the manufacture of a medicament in the prevention or in the treatment of depression.
- The use according to claim 8 in the manufacture of a medicament in the prevention or in the treatment of anxiety.
- A method for the prevention or the treatment of CNS disorders and related medical disturbances comprising administration, to a host in need of such treatment, an effective amount of the salt according to any one of claims 1 to 3.

- 12. A method according to claim 11 for prevention or the treatment of 5-HT_{1A} receptor antagonist activity related CNS disorders and medical disturbances.
- 13. A method according to claim 12 for the prevention or the treatment of depression.
- 14. A method according to claim 12 for the prevention or the treatment of anxiety.
- 15. A process for the manufacture of the salt as defined in any one of claims 1 to 3 characterized by the following consecutive steps:
 - i) dissolving (R)-3-N,N-dicyclobutylamino-8-fluoro-3,4-dihydro-2H-1-benzopyran-5-carboxamide in an appropriate solvent, optionally by heating,
 - ii) adding (2R, 3R)-tartaric acid, respectively, dissolved in an appropriate aqueous organic solvent or non-aqueous organic solvent,
 - iii) allowing the solution obtained to stand cold to crystallize,
 - iv) optionally recrystallizing in an appropriate aqueous organic solvent, if a non-aqueous organic solvent is used in step ii), to obtain the salt defined in any one of claims 2 or 3.
- 16. A process for the manufacture of the salt as defined in claims 2 to 3 characterized by recrystallizing (R)-3-N,N-dicyclobutylamino-8-fluoro-3, 4-dihydro-2H-benzopyran-5-carboxamide hydrogen (2R,3R)-tartrate in an appropriate aqueous organic solvent.
- 17. A process according to any one of the claims 15 or 16, wherein the aqueous organic solvent is aqueous acetone.

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REQUEST

For receiving Office u		
International Application No.		
International Filing Date		
Name of receiving Office and "PCT Interr	national Application"	

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.	Name of receiving Office	and "PCT International Application"		
	Applicant's or agent's file (if desired) (12 characters	reference maximum) J 1747-1 WO		
Box No. I TITLE OF INVENTION	· !			
A NEW SALT				
Box No. II APPLICANT				
Name and address: (Family name followed by given name; for a legal The address must include postal code and name of country. The country of Box is the applicant's State (i.e. country) of residence if no State of residence	of the address indicated in this	This person is also inventor.		
ASTRA AKTIEBOLAG S-151 85 Södertälje		Telephone No. +46 8 553 260 00		
Sweden		Facsimile No.		
		+46 8 553 288 20		
		Teleprinter No.		
State (i.e. country) of nationality:	State (i.e. country) of re	sidence:		
This person is applicant for the purposes of: all designated States all designated the United		United States America only the States indicated in the Supplemental Box		
Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)				
Name and address: (Family name followed by given name; for a legal The address must include postal code and name of country. The country Box is the applicant's State (i.e. country) of residence if no State of residence if	entity, full official designation. of the address indicated in this ence is indicated below.)	This person is: applicant only applicant and inventor inventor only (If this check-box is marked, do not fill in below.)		
State (i.e. country) of nationality: SE	State (i.e. country) of re	sidence: SE		
	ed States except States of America the	United States the States indicated in the Supplemental Box		
Further applicants and/or (further) inventors are indicated	on a continuation sheet.			
Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE				
The person identified below is hereby/has been appointed to act of the applicant(s) before the competent International Authoritie	on behalf s as:	gent common representative		
Name and address: (Family name followed by given name; for a legal The address must include postal code and name	entity, full official designation. of country.)	Telephone No.		
Patent Department		+46 8 553 260 00		
Astra Aktiebolag S-151 85 Södertälje		Facsimile No. +46 8 553 288 20		
Sweden		Teleprinter No.		
Mark this check-box where no agent or common represents	ative is/has been appointed	and the space above is used instead to		
indicate a special address to which correspondence should	be sent.	See Notes to the request form		

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Continuation of Box No. III FURTHER APPLICANTS AN	D/OR (FURTHER) INV	ENTORS
If none of the following sub-boxes is used, t	this sheet is not to be inclu	uded in the request.
Name and address: (Family name followed by given name: for a legal en The address must include postal code and name of country. The country of Box is the applicant's State (i.e. country) of residence if no State of residence SOHN, Daniel D Astra Arcus AB S-151 85 Södertälje Sweden	tity, full official designation. the address indicated in this ce is indicated below.)	This person is: applicant only applicant and inventor inventor only (If this check-box is marked, do not fill in below.)
State (i.e. country) of nationality:	State (i.e. country) of res	
US		SE TO SECOND TO
This person is applicant for the purposes of: all designated the United States all designated the United States	States except the of America	United States America only the States indicated in the Supplemental Box
Name and address: (Family name followed by given name; for a legal en The address must include postal code and name of country. The country of the Box is the applicant's State (i.e. country) of residence if no State of residence	nity, full official designation. the address indicated in this ce is indicated below.)	This person is: applicant only applicant and inventor inventor only (If this check-box is marked, do not fill in below.)
State (i.e. country) of nationality:	State (i.e. country) of res	sidence:
This person is applicant all designated all designated	States except the	United States
for the purposes of: States the United States	tes of America of A	America only the Supplemental Box
Name and address: (Family name followed by given name; for a legal ent The address must include postal code and name of country. The country of t Box is the applicant's State (i.e. country) of residence if no State of residence	rity, full official designation. he address indicated in this re is indicated below.)	This person is: applicant only applicant and inventor inventor only (If this check-box is marked, do not fill in below.)
State (i.e. country) of nationality:	State (i.e. country) of res	sidence:
This person is applicant for the purposes of: all designated the United States all designated the United States	States except the tes of America of A	United States America only the States indicated in the Supplemental Box
Name and address: (Family name followed by given name; for a legal ent The address must include postal code and name of country. The country of t Box is the applicant's State (i.e. country) of residence if no State of residence	ity, full official designation. he address indicated in this ce is indicated below.)	This person is: applicant only applicant and inventor inventor only (If this check-box is marked, do not fill in below.)
State (i.e. country) of nationality:	State (i.e. country) of res	idence:
This person is applicant all designated for the purposes of:		United States the States indicated in the Supplemental Box
Further applicants and/or (further) inventors are indicated or	n another continuation she	et.

Box No.V	DESIGNATION OF STATES
The followin	g designations are hereby made under R

The following designations are hereby made under Rule 4.9(a) (mark the applicable check-boxes; at least one must be marked):

	Re	gion	al P	atent
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- AP ARIPO Patent: GH Ghana, GM Gambia, KE Kenya, LS Lesotho, MW Malawi, SD Sudan, SZ Swaziland, UG Uganda, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT
- EA Eurasian Patent: AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakhstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT
- EP European Patent: AT Austria, BE Belgium, CH and LI Switzerland and Liechtenstein, DE Germany, DK Denmark, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, and any other State which is a Contracting State of the European Patent Convention and of the PCT
- OA OAPI Patent: BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT (if other kind of protection or treatment desired, specify on dotted line)

Nation	nal P	atent (if other kind of protection or treatment desired,	Speci	ify on	dotted line)
X		Albania	X		Lithuania
<u> </u>	AM	Armenia	X	LU	Luxembourg
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×	ΑU	Australia	X	MD	Republic of Moldova
X	ΑZ	Azerbaijan	X		Madagascar
X	BA	Bosnia and Herzegovina	X		The former Yugoslav Republic of Macedonia
X	BB	Barbados	_		
X	\mathbf{BG}	Bulgaria	X	MN	Mongolia
X	BR	Brazil	X	MW	Malawi
X	\mathbf{BY}	Belarus	X	MX	Mexico
X	CA	Canada	X	NO	Norway
X	CH:	and LI Switzerland and Liechtenstein	X	NZ	New Zealand
X	CN	China	X	PL	Poland
X	CU	Cuba	X	PT	Portugal
X	\mathbf{CZ}	Czech Republic	X	RO	Romania
X	DE	Germany	X	RU	Russian Federation
X	DK	Denmark	X	SD	Sudan
X	EE	Estonia	X	SE	Sweden
X	ES	Spain	X	SG	Singapore
X	FI	Finland	X	SI	Slovenia
X	GB	United Kingdom	X	SK	Slovakia
X	GE	Georgia	X	SL	Sierra Leone
X	GH	Ghana	X	TJ	Tajikistan
\mathbf{X}	GM	Gambia	X	TM	Turkmenistan
X	GW	Guinea-Bissau	X	TR	Turkey
X	HU	Hungary	X	TT	Trinidad and Tobago
X	ID	Indonesia	X	UA	Ukraine
X	IL	Israel	X	UG	Uganda
X	IS	Iceland	X	US	United States of America
X	JP	Japan			
X		Kenya	X		Uzbekistan
X		Kyrgyzstan	X		Viet Nam
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X		Republic of Korea	Che	ck-box	ces reserved for designating States (for the purposes of
X		Kazakhstan	a na	tional	patent) which have become party to the PCT after f this sheet:
	_	Saint Lucia			Cyprus
(₹)		Sri Lanka	=		
	_	Liberia			
X	LS	Lesotho	<u> 니</u>		

In addition to the designations made above, the applicant also makes under Rule 4.9(b) all designations which would be permitted under the PCT except the designation(s) of

The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. (Confirmation of a designation consists of the filing of a notice specifying that designation and the payment of the designation and confirmation fees. Confirmation must reach the receiving Office within the 15-month time limit.)

Sheet No. 4

Box No. VI PRIORITY CLAIM Further priority claims are indicated in the Supplemental Box									
The priority of the following earlier application(s) is hereby claimed:									
Country (in which, or for which, the application was filed)	Filing Date (day/month/year	Application	No. (c	Office of filing only for regional or reational application)					
item(1)	30 May 1997								
Sweden	(30.05.1997)	9702066-3							
item(2)									
item (3)									
Mark the following check-box if the certified copy of the earlier application is to be issued by the Office which for the purposes of the present international application is the receiving Office (a fee may be required): The receiving Office is hereby requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) identified above as item(s): (1)									
Box No. VII INTERNATIO	NAL SEARCHING AU	ГНОRITY							
Choice of International Searching Authority (ISA) (If two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used): Earlier search Fill in where a search (international, international-type or other) by the International Searching Authority has already been carried out or requested and the Authority is now requested to base the international search, to the extent possible, on the results of that earlier search. Identify such search or request either by reference to the relevant application (or the translation thereof) or by reference to the search request:									
Country (or regional Office):	Date (day/month/ye		Number:	n request.					
Sweden	22 September	r 1997 (22.09.1997)	ITS SE 97/00	0696					
Box No. VIII CHECK LIST									
This international application the following number of sheet 1. request : 4		ternational application is accomp separate signed 5.	anied by the item(s) to						
2. description : 9	sheets 2.	copy of general 6.	separate ind deposited mid	ications concerning					
3. claims : 3	sheets	statement explaining	`	nd/or amino acid					
4. abstract : 1	sheets 3.	lack of signature 7.	sequence list						
5. drawings : 2 Total : 19	sheets 4.	priority document(s) 8. identified in Box No. VI as item(s):	other (specify						
Figure No. 2 of the drawings (if any) should accompany the abstract when it is published.									
Box No. IX SIGNATURE OF APPLICANT OR AGENT Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request)									
Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reduing the request). Södentälje, 14 May 1998									
Sala Shoul									
Britta Samuelsson Patent Department of Astra Aktiebolag									
For receiving Office use only —									
Date of actual receipt of the international application:		y		2. Drawings:					
 Corrected date of actual rec timely received papers or dr the purported international a 	awings completing			received:					
Date of timely receipt of the corrections under PCT Arti-	e required cle I 1(2):			notreceived:					
5. International Searching Aut specified by the applicant:	hority ISA /	6. Transmittal of suntil search fee	earch copy delayed is paid						
For International Bureau use only									
Date of receipt of the record copy by the International Bureau:									